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Clinical analysis of fungal keratitis according to prior topical steroid use: A retrospective study

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Research Article

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Abstract

Background: To compare the clinical characteristics and treatment outcomes of microbiologically-proven fungal keratitis between prior topical steroid users (PS) and no prior topical steroid users (NPS).

Methods: Eighty-three cases with microbiologically-proven fungal keratitis between January 2000 and December 2016 were reviewed retrospectively. Diagnosis of fungal keratitis was made through potassium hydroxide smear, culture, PCR, or biopsy. Baseline epidemiology, predisposing factors and clinical characteristics, microbiological profiles, and treatment outcomes were compared between the PS and NPS groups. The treatment failure was defined as any case with complications or requiring surgery. The risk factors for treatment failure were evaluated on the bases of the total cohort and analyzed using multivariate logistic regression.

Results: A total of 30 cases with PS group and 53 cases with NPS group were included. No significant differences were observed in mean age, sex, occupation, and baseline clinical characteristics between the two groups. Differences were observed between the PS and NPS groups in the cases of previous ocular surface disease (43.3% vs. 22.6%, p=0.048), identified fungal isolates (53.3% vs. 26.4%, p=0.014), and diagnosed by repeat microbiological tests (40.0% vs. 17.0%, p=0.020). *Candida* was the most common organism in both groups (6 cases, respectively), while the *Aspergillus* (4 cases) was found only in the PS group (p=0.015). Regarding treatment outcomes, the use of voriconazole (topical 10% vs. 0%, p=0.044; systemic 23.3% vs. 1.9%, p=0.003), surgical intervention (43.3% vs. 20.8%, p=0.029) and treatment failure (46.7% vs. 22.6%, p=0.023) were more common in the PS group than in the NPS group. The risk factors for treatment failure were hypopyon (odds 5.95, p=0.003), prior topical steroid use (odds 3.45, p=0.034), and non-vegetable corneal trauma (odds 4.46, p=0.037).

Conclusions: The PS group was more associated with previous ocular surface disease, and no significant differences were observed in the baseline clinical characteristics between the two groups. Diagnosis was more difficult and treatment results were worse in the PS group in this study. Repeat microbiological tests can be helpful in diagnosing fungal infections especially in the prior topical steroid used group.

Keywords: Fungal ocular infection, Steroids, Ulcerative keratitis.

Background

Fungal keratitis is an important cause of severe sight-threatening disease and has been reported to account for about 50% of all microbial keratitis cases requiring therapeutic penetrating keratoplasty [1]. Fungal keratitis is a challenging disease to diagnose and treat, it is often confused with other infectious keratitis because there is insufficient clinical and microbiological evidence during the early stages of keratitis, thus leading to delayed treatment. In the aspect of treatment, fungal keratitis has been reported to be relatively worse than bacterial keratitis [2]. Furthermore, there are few commercialized topical antifungal agents, and most of these agents cannot penetrate the cornea effectively [3, 4].

The risk factors for fungal keratitis include ocular trauma, ocular surface disease, contact lens use, topical steroid use, and systemic immunosuppression [5, 6]. Among these, the prior use of topical corticosteroids has been shown to be a clinically important factor because it can exacerbate the infection [7]. The use of topical steroids in the early stages of infectious keratitis makes it difficult to judge clinical progression because the immune-inflammatory response in the corneal stroma is temporarily improved and the immune response of the host is decreased [8].

Despite these clinical importance, clinical analysis of fungal keratitis according to prior topical steroid use is rarely reported. Therefore, we conducted a comparative study of patients with microbiologically-proven fungal keratitis according to prior topical steroid use at a tertiary referral center in South Korea. The aim of this study was to compare epidemiology, predisposing factors, clinical characteristics, microbiological profiles, and treatment outcomes in patients with microbiologically-proven fungal keratitis according to prior topical steroid use.

Methods

This study was conducted at the Yeungnam University Hospital, a tertiary referral center in South Korea. We retrospectively reviewed medical records of microbiologically-proven fungal keratitis cases between January 2000 and December 2016. Microbiologically-proven 83 cases of fungal keratitis were enrolled in this study. For the purpose of this study, the total cases were divided into two groups: those with prior topical steroid use before the diagnosis of fungal keratitis as PS group (30 cases, 36.1%), and those with no prior topical steroid use before diagnosis as NPS group (53 cases, 63.9%). The clinical outcomes were assessed at the end of 3 months or at the completion of treatment. This study was approved by the Institutional Review Board of the Yeungnam University Hospital (IRB No. 2018-11-015), Republic of Korea, and complied with the principles outlined in the Declaration of Helsinki.

Baseline epidemiology, predisposing factors, clinical characteristics, microbiological profiles, and treatment outcomes were evaluated and compared between the PS and NPS groups. The epidemiologic characteristics included age, sex, occupation, and symptom duration. The symptom duration defined as the interval from the onset of symptoms to the time of initial presentation. The predisposing factors included previous ocular surface disease (OSD), previous ocular surgery, underlying systemic disease, corneal trauma, and use of contact lens. The initial clinical characteristics included the location, size of the corneal lesion, the presence of the hypopyon, and presenting best-corrected visual acuity (BCVA) using the Snellen test. The corneal lesions were divided into central or peripheral lesions based on the half radius of the cornea. The size of corneal lesions was calculated based on the size of the corneal epithelial defect [9].

All of patients were performed baseline microbiological test such as 10% potassium hydroxide (KOH) smear and culture. Repeated microbiological test was defined as any microbiological test performed additionally after the baseline test. We investigated whether the fungal keratitis was first diagnosed in the baseline or repeated test. All patients were treated with topical/systemic antifungal and antibiotic agents.

Used topical antifungal agents were 0.15% amphotericin B, 5% natamycin, and 1% voriconazole. Used topical antibiotics were third- or fourth-generation fluoroquinolone eyedrops, 2% tobramycin, and 5% ceftazidime. The types of used topical antifungal eyedrops and systemic antifungal agents were analyzed. For the PS group, we gradually tapered the use of steroids adequately. Treatment outcomes were evaluated by epithelial healing time (EHT), complication, surgical intervention, and final BCVA. Treatment failure was defined as the occurrence of complications or surgical treatment.

The data were statistically analyzed using the Statistical Package for the Social Sciences 20.0 (IBM, Armonk, NY, USA). Chi-squared test and Fisher's exact test were used for categorical data. Independent *t*-tests were used for comparison of mean values. Statistical significance was defined as $p < 0.05$. The risk factors for treatment failure were analyzed using logistic regression analysis. In the univariate analysis, an independent variable with a $p < 0.1$ was included in the multivariate analysis and a variable with a final $p < 0.05$ was considered a significant risk factor.

Result

Baseline epidemiology, predisposing factors, and clinical characteristics

The baseline epidemiology, predisposing factors, and clinical characteristics are detailed in Table 1. For the total patients, mean age was 63.0 ± 14.3 years and male sex was 57.8%. Agricultural workers were the most common occupations in both groups. There were no significant differences in mean age, sex, and mean symptom duration between the two groups.

Concerning the predisposing factors, corneal trauma was the most common in both groups with no significant difference. The ratios of previous OSD ($p = 0.048$) and previous ocular surgery ($p = 0.139$) were higher in the PS group. Herpetic keratitis was the most common previous OSD in both groups.

In the initial clinical characteristics, central corneal lesions were more common than peripheral ones in both groups. There were no differences in the location of corneal lesions and hypopyon between the two groups. The cases with epithelial defect ≥ 10 mm^2 ($p = 0.228$) and initial BCVA < 0.1 ($p = 0.194$) were slightly higher in the PS group, but no statistically significant difference between the two groups.

Microbiological test results

Table 2 shows the microbiological test results. Sixty-two cases (74.7%) were diagnosed by baseline microbiological test and 21 cases (25.3%) were diagnosed by repeated test. The cases of diagnosed by baseline microbiological test was less common in the PS group than in the NPS group (60% vs. 83%, $p = 0.020$).

For the total patients, thirty fungal isolates were identified in 30 eyes. The cases of identified fungal isolates was more common in the PS group when compared with the NPS group (16/30, 53.3% vs. 14/53, 26.4%, $p = 0.014$). The most common fungal isolates were the *Candida* species (12 cases, 40%), followed

by *Fusarium* species (8 cases, 26.7%), and *Aspergillus* species (4 cases, 13.3%). There was no difference between the two groups in the distribution of *Candida* and *Fusarium* species, while the *Aspergillus* species was found only in the PS group.

Treatment outcome

Sixty-three cases (75.9%) received topical antifungal monotherapy, while 20 cases (24.1%) received a combined antifungal treatment. There were no differences in the topical antifungal agents used between the two groups, except for the use of voriconazole/natamycin combination (used in 10% of cases in the PS group vs. 0% in the NPS group, $p = 0.044$). For systemic antifungal agents, fluconazole was the most commonly used (52 cases, 62.7%), followed by amphotericin B (25 cases, 30.1%). The use of systemic voriconazole was significantly higher in the PS group ($p = 0.003$). In the PS group, the mean EHT was slightly longer ($p = 0.165$), and the cases with final BCVA < 0.1 were slightly higher ($p = 0.169$) when compared with the NPS group (Table 3).

Corneal perforation was the most common complication (15 cases) in the total patients, followed by endophthalmitis (3 cases). The proportion of corneal perforation was slightly higher in the PS group ($p = 0.126$). Twenty-four cases (28.9%) required surgical intervention and was significantly higher in the PS group ($p = 0.029$). Amniotic membrane transplantation was significantly more common in the PS group ($p = 0.011$). There was no difference in the evisceration/enucleation rate between the two groups. The proportion of treatment failure was significantly higher in the PS group ($p = 0.023$) (Table 3).

Risk factors for treatment failure

In multivariate logistic regression, hypopyon (OR 5.95, 95% CI 1.86-19.00, $p = 0.003$), prior topical steroid use (OR 3.45, 95% CI 1.10-10.81, $p = 0.034$), and non-vegetable corneal trauma (OR 4.46, 95% CI 1.10-18.14, $p = 0.037$) were the significant risk factors for treatment failure in the total patients (Table 4).

Discussion

In this study, the proportion of cases with prior topical steroid use history was 36.1%. Previous OSD and previous ocular surgery history were higher in the PS group likely because steroids were used for treating their underlying causes. A previous Korean study reported that 14.1% of fungal keratitis cases used prior topical steroids [10], while other studies have reported similar proportions, ranging from 13 to 44% [11-13].

The types and distribution of fungi in fungal keratitis vary according to geography, climate, and socioeconomic characteristics. In this study, the most commonly identified organism was *Candida* species in both groups (20% in PS and 11.3% in NPS) and followed by *Fusarium* species in total patients. In terms of most commonly identified organisms, *Candida* species of our results is similar to the results reported in Pennsylvania, USA (45.8%) [14], Denmark (52%) [11], London, UK (60.6%) [15], and France (58%) [16]. In contrast, many studies such as North China (73.3%) [17], a multicenter study in Korea (29%)

[10], central China (30.6%) [18], Mexico City (37.2%) [19], Florida, USA (41%) [20], and South India (37.2%) [21] reported that the *Fusarium* was the most commonly identified organism. In addition, some reports such as Saudi Arabia (27.2%) and North India (41%) showed that *Aspergillus* was the most commonly identified organism [22]. Regarding to *Aspergillus,* our study showed that it was found only in the PS group. This result can be supported by the study of Tony et al., who had reported that corticosteroids promote the growth of *Aspergillus* [23].

Since the delayed diagnosis of fungal keratitis has a significant adverse impact on treatment outcomes, the importance of early suspicion and rapid diagnosis of fungal keratitis has been reported in many studies [24, 25]. We expected that the PS group had more severe initial clinical characteristics when compared with the NPS group, but our study found that there were no significant differences in initial clinical characteristics between the two groups. We thought this result is related to the inflammation-masking effect of previous topical steroids in early clinical characteristics of keratitis. This suggests to us that the use of prior topical steroid likely masked the early clinical characteristics of fungal keratitis thereby delaying its suspicion and early diagnosis. Therefore, it is critical that efforts aimed at making a diagnosis, including culture of corneal scrapings and KOH smear, be done at the time of initial presentation.

This study found that the cases of diagnosed through baseline tests was less common in the PS group when compared with the NPS. This result makes it possible to suspect that the use of prior topical steroids may be affect the positive rate of the baseline test. One possible hypothesis is due to less possibility of microorganism detection in necrotic tissue according to more aggressive inflammatory response associated with the steroid-withdrawal rebound effect in the steroid-used group. Another possible hypothesis might be related to our speculation that vertically located hyphae penetrate deeply into the corneal stroma and the surface hyphae are relatively less distributed in the steroid-used group based on Panda et al.'s study [26]. However, the relationship between the use of prior topical steroids and the positive rate of culture was rarely reported and further studies will be needed.

The cases of identified fungal isolates was more common in the PS group in our study when compared with the NPS. One of the interpretations associated with this result is that steroid use can promotes fungal proliferation, hence enhancing its identification. Second, additional laboratory testing, such as culture and histopathology examinations, was more performed in the PS group since these patients underwent more surgeries when compared with the NPS group. Therefore, the higher identification rate of fungal isolates in the PS group could be related to the increased effort in finding these organisms via repeated testing. In other study related to repeat microbiological testing, Kathryn et al. reported the significance and the utility of repeat cultures in fungal keratitis [27, 28]. These studies found that repeat culture positivity is an important predictor of poor clinical outcome in severe fungal keratitis and reported that repeat cultures provide important additional information to assess response to treatment. Thus, repeated microbiological test such as KOH smear, culture, and biopsy should be considered to detect fungal organisms when there is no sufficient response to initial treatment.

There was no significant difference in the type of antifungal agents used between the two groups, but for topical and systemic voriconazole use which was significantly higher in the PS group. In our institute, we have added the use of topical and systemic voriconazole when there is no response to conventional antifungal therapy. The significantly higher use of topical and systemic voriconazole in the PS group indicates that the treatment response was worse than expected in this PS group. The PS group had significantly higher surgical intervention and treatment failure when compared with the NPS group. This is consistent with other studies, and the topical steroids use in fungal keratitis lead to worse outcomes [29, 30]. These results highlight the side effects of prior topical steroid use in the setting of fungal keratitis.

Evisceration/enucleation was performed in 13.3% of the total patients, similar to the proportion reported in a multicenter study in Korea (10.6%) [10]. The authors expected that there would be higher incidence of evisceration/enucleation in the group of prior topical steroid use, but we found no significant difference was observed between the PS and the NPS group in this study. The frequency of evisceration/enucleation within 1 month was relatively higher in the NPS group than in the PS group (5/7, 71% vs. 2/4, 50%, p = 0.576). Therefore, we thought that the evisceration/enucleation was more associated with initial clinical severity than the prior topical steroid use itself through this study. In addition, hypopyon (64%) was more common in the patients who underwent evisceration/enucleation and was the only significant risk factor of evisceration/enucleation (OR 4.88, 95% CI 1.28-18.56, p = 0.020).

In this study, significant risk factors for treatment failure included hypopyon, prior topical steroid use, and non-vegetable corneal trauma. Risk factors for treatment failure reported in other studies varied and were associated with severe initial clinical characteristics, such as large epithelial defect size, hypopyon, and prior topical steroid use [31-33]. In this study, non-vegetable corneal trauma was a significant risk factor for treatment failure. This result was thought to be associated with the difference between non-vegetable trauma and vegetable trauma in the proportion of previous OSD (42.6% vs. 6.9%, p = 0.001) and fungal isolates distribution (*Candida*, 11 vs. 1 case; *Aspergillus*, 4 vs. 0 case).

The various effects of steroids on the fungal keratitis reported in several studies include: First, suppression of inflammation and subsequent growth promotion of the fungal genus. Second, fungal keratitis is more virulent when the hyphae in corneal tissue sections are found at a right angle than when they are parallel to the corneal stroma, and also the vertically oriented hyphae are more commonly observed in the eyes of patients who used steroid [26]. Third, steroid use has been associated with decreased response to antifungal agents, and steroid treatment itself is a known risk factor for fungal infection [8, 30, 34]. In addition to the aggravation of infection, steroids delay epithelial regeneration and have quite severe inflammatory side effects [35-38]. Therefore, it should be emphasized that early steroid use is contraindicated when an infection is suspected, and clinicians should be cautious when prescribing steroids for suspected cases of infectious keratitis.

This study has some limitations. First, the included cases were confined to the patients of one tertiary hospital, therefore the results of this study cannot be generalized. Second, since it is a retrospective study,

we could not accurately identify the potency and dose of topical steroids for patients referred from their primary care hospital. Third, only the patients with microbiological evidence of fungal keratitis were enrolled in this study while cases without such evidence were excluded, even if fungal keratitis was highly suspected. Despite such limitations, this study has important clinical value, illuminating the risk and side effects of prior topical steroid use in clinical practice.

Conclusions

In conclusion, 36.1% of the patients used topical steroids prior to the diagnosis of fungal keratitis. There was no significant difference in initial clinical characteristics between the two groups. In baseline characteristics, the PS group was more associated with the cases of identified fungal isolates (p = 0.014), *Aspergillus* species (p = 0.015), previous OSD (p = 0.048), and diagnosed by repeat microbiological tests (p = 0.020) when compared with the NPS group. With respect to treatment outcomes, the use of voriconazole (topical, p=0.044; systemic, p=0.003), surgical intervention (p = 0.029) and treatment failure (p = 0.023) were more common in the PS group. The risk factors for treatment failure in the total patients were hypopyon (p = 0.003), the prior use of topical steroid (p = 0.034), and non-vegetable corneal trauma (p = 0.037). Diagnosis was more difficult and treatment results were worse in patients with fungal keratitis who had prior topical steroid use. Therefore, more attention should be paid to the use of steroids in clinical practice. In addition, repeating microbiological tests can be helpful in diagnosing fungal infections, especially in the setting of prior steroids use.

Abbreviations

BCVA, Best corrected visual acuity; CI, Confidence interval; EHT, Epithelial healing time; NPS, no prior topical steroid use group; OR, Odds ratio; OSD, Ocular surface disease; PCR, Polymerase chain reaction; PS, prior topical steroid use group

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Yeungnam University Hospital, South Korea (file no. YUMC 2018-11-015), and complied with the principles outlined in the Declaration of Helsinki. Institutional Review Board of our institution allowed us "waiver of informed consent" because it is determined that obtaining consent from a human subject of research is impracticable in the course of research and the risk to a human subject of research is very low even if the project is exempted from consent, as per the Bioethics and Safety Act of the Republic of Korea (Chapter 3, Article 16, Paragraph 3, Act No. 14839. Enforcement Date 26. July 2017.).

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

CH Cho: literature research, drafting, language editing, and critical revision.

SB Lee: patient interaction, patient diagnosis, language editing, and critical revision.

All authors read and approved the final manuscript.

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Tables

Table 1. Baseline epidemiology, predisposing factors and clinical characteristics of fungal keratitis according to prior topical steroid use

Characteristics	PS (n=30)	NPS (n=53)	*p*-value
Epidemiology			
Male sex	19 (63.3)	29 (54.7)	0.445
Age, years	60.2 ± 14.9	64.6 ± 13.9	0.180
Occupation			
Agriculture	14 (46.7)	25 (47.2)	0.965
Non-agriculture	16 (53.3)	28 (52.8)	
Symptom duration, days	19.7 ± 15.4	15.0 ± 13.8	0.154
Predisposing factors			
Corneal trauma	21 (70.0)	43 (81.1)	0.246
Vegetable matter or wood	8 (26.7)	21 (39.6)	0.234
Soil or water	9 (30.0)	16 (30.2)	0.986
Other trauma	4 (13.3)	6 (11.3)	1.000*
Previous OSD	13 (43.3)	12 (22.6)	0.048
Herpetic keratitis	7 (23.3)	5 (9.4)	0.108*
Punctate keratopathy	3 (10.0)	2 (3.8)	0.346*
Old corneal opacity	2 (6.7)	3 (5.7)	1.000*
Other keratopathy†	1 (3.3)	2 (3.8)	1.000*
Contact lens wear	1 (3.3)	4 (7.5)	0.649*
Previous ocular surgery	10 (33.3)	10 (18.9)	0.139
Systemic disease	12 (40.0)	21 (39.6)	0.973
Diabetes mellitus	4 (13.3)	10 (18.9)	0.518
Hypertension	7 (23.3)	12 (22.6)	0.943
Initial clinical characteristics			
Central corneal lesion	22 (73.3)	42 (79.2)	0.538
Epithelial defect size ≥ 10 mm^2	13 (43.3)	16 (30.2)	0.228
Hypopyon	9 (30.0)	17 (32.1)	0.845
Initial BCVA < 0.1, Snellen	20 (66.7)	27 (51.9)	0.194

Values are presented as mean ± standard deviation or number (%).

PS=group of prior topical steroid use; NPS=group of no prior topical steroid use; OSD=ocular surface disease; BCVA=best corrected visual acuity.

*The *p*-value was calculated using Fisher's exact test

†Include neurotrophic keratopathy (PS), bullous keratopathy (NPS), and exposure keratopathy (NPS).

Table 2. Microbiological test results according to prior topical steroid use

	PS (n=30)	NPS (n=53)	*p*-value
Microbiological test results*			
Diagnosed by baseline microbiological test	18 (60.0)	44 (83.0)	0.020
Diagnosed by repeated microbiological test†	12 (40.0)	9 (17.0)	
Identified fungal isolates‡	16 (53.3)	14 (26.4)	0.014
Candida species	6 (20.0)	6 (11.3)	0.337#
Fusarium species	3 (10.0)	5 (9.4)	1.000#
Aspergillus species	4 (13.3)	0 (0.0)	0.015#
Syncephalastrum species	0 (0.0)	1 (1.9)	1.000#
Alternaria species	1 (3.3)	0 (0.0)	0.361#
Cryptococcus species	1 (3.3)	0 (0.0)	0.361#
Acremonium species	1 (3.3)	0 (0.0)	0.361#
Unknown species	0 (0.0)	2 (3.8)	0.533#
KOH smear positive	20 (66.7)	46 (86.8)	0.029
Identified fungal isolates and KOH smear positive	6 (20.0)	7 (13.2)	0.532#

Values are presented as number (%).

PS=group of prior topical steroid use; NPS=group of no prior topical steroid use; KOH=potassium hydroxide; PCR=polymerase chain reaction.

*Defined as positive result if at least one of the following is included: (a) positive fungal culture from a corneal specimen, (b) positive identification of fungal elements on a 10% KOH smear, (c) positive identification of fungal elements on multiplex PCR, or (d) histopathology showing presence of fungal elements.

†Repeat microbiological tests were performed in 15 cases (15/30, 50%) of the PS group and 16 cases (16/53, 30.2%) of the NPS group.

#The *p*-value was calculated using Fisher's exact test.

‡Identified by culture, multiplex PCR, and biopsy.

Table 3. Treatment outcome of fungal keratitis according to prior topical steroid use

Characteristics	PS (n=30)	NPS (n=53)	*p*-value
Medical treatment: topical			
Antifungal agent monotherapy	20 (66.7)	43 (81.1)	0.139
Amphotericin B	8 (26.7)	19 (35.8)	0.391
Natamycin	12 (40.0)	24 (45.3)	0.641
Combined antifungal agents	10 (33.3)	10 (18.9)	0.139
Amphotericin B/ natamycin	7 (23.3)	10 (18.9)	0.628
Voriconazole/ natamycin	3 (10.0)	0 (0.0)	0.044*
Medical treatment: systemic†			
Terbinafine	5 (16.7)	4 (7.5)	0.273*
Itraconazole	1 (3.3)	4 (7.5)	0.649*
Fluconazole	16 (53.3)	36 (67.9)	0.187
Amphotericin B	8 (26.7)	17 (32.1)	0.606
Voriconazole	7 (23.3)	1 (1.9)	0.003*
Treatment outcome			
Epithelial healing time, days‡	44.6 ± 50.5	29.6 ± 27.9	0.165
Final BCVA < 0.1, Snellen#	18 (60.0)	23 (44.2)	0.169
Complications			
Corneal perforation	8 (26.7)	7 (13.2)	0.126
Endophthalmitis	2 (6.7)	1 (1.9)	0.295*
Surgical intervention	13 (43.3)	11 (20.8)	0.029
AMT	9 (30.0)	4 (7.5)	0.011*
Evisceration/enucleation	4 (13.3)	7 (13.2)	1.000*
Conjunctival flap	6 (20.0)	4 (7.5)	0.157*
Penetrating keratoplasty	0 (0.0)	1 (1.9)	1.000*
Duration of hospitalization, days§	15.6 ± 6.3	13.0 ± 6.0	0.070
Treatment failure¶	14 (46.7)	12 (22.6)	0.023
Time to evisceration/enucleation < 1 month**	2/4 (50.0)	5/7 (71.4)	0.576

Values are presented as mean ± standard deviation or number (%).

PS=group of prior topical steroid use; NPS=group of no prior topical steroid use; BCVA=best corrected visual acuity; AMT=amniotic membrane transplantation.

*The *p*-value was calculated using Fisher's exact test.

†Percent do not add to 100% because some cases had combined systemic medications.

‡Total n=71: cases with persistent epithelial defect were excluded. (3 cases in PS, 9 cases in NPS)

#The final BCVA was assessed at the end of 3 months or at the completion of treatment.

§Total n=77: cases of outpatients were excluded (2 cases in PS, 4 cases in NPS)

¶Defined as the occurrence of complication or surgical intervention.

**Percentages and statistical values were calculated within the group of underwent evisceration/enucleation.

Table 4. Risk factors for treatment failure in fungal keratitis using univariate and multivariate logistic regression analysis

Variables	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Female sex	1.27	0.50-3.23	0.620			
Age ≥ 60 years	1.80	0.62-5.21	0.277			
Non-agricultural occupation	2.10	0.80-5.49	0.130			
Non-vegetable corneal trauma	3.22	1.13-9.20	0.029	4.46	1.10-18.14	0.037
Prior topical steroid use	2.99	1.14-7.84	0.026	3.45	1.10-10.81	0.034
Previous OSD	2.90	1.08-7.80	0.035			
Previous ocular surgery	1.25	0.43-3.62	0.685			
Diabetes mellitus	2.63	0.81-8.51	0.106			
Symptom duration ≥ 10 days	1.34	0.52-3.46	0.543			
Central corneal lesion	1.02	0.34-3.06	0.978			
Epithelial defect size ≥ 10 mm^2	2.56	0.98-6.70	0.055			
Hypopyon	5.70	2.06-15.80	0.001	5.95	1.86-19.00	0.003
Initial BCVA < 0.1, Snellen	4.85	1.60-14.67	0.005			
Diagnosed by repeated microbiological test	2.00	0.71-5.65	0.191			
Topical antifungal monotherapy	1.86	0.55-6.29	0.318			

OR=odds ratio; CI=confidence interval; OSD=ocular surface disease; BCVA=best corrected visual acuity. Treatment failure was defined as the occurrence of complication or surgical intervention.

*Multivariate logistic regression analysis was performed using the backward-conditional method for the factors with a *p*-value < 0.1 in univariate logistic regression analysis.